SPECIFICATION

PATCHES CONTAINING TUROBUTEROL

TECHNICAL FIELD

The present invention relates to a dermally absorbable type patch containing turobuterol.

BACKGROUND ART

Various dermally absorbable type preparations containing turobuterol have been recently proposed as preparations making up the demerits of the oral preparation containing turobuterol (See Japanese Patent Publication A 11-228395, Japanese Patent No. 2753800 (Japanese Patent Publication A 7-285854), WO 97/14411 and Japanese Patent No. 2633089 (Japanese Patent Publication A 5-194202)).

A patch prepared by dissolving turobuterol into an adhesive has such a demerit as the duration necessary to sustain its effective serum concentration is not attained.

Therefore, techniques to increase the concentration of turobuterol or to contain much amount of it by thickening an adhesive layer have been tried.

For example, in Japanese Patent Publication A 11-228395, a turobuterol-patch which has a structure to fully dissolve turobuterol are proposed. However, when such a patch is preserved for a long time due to the high concentration of turobuterol, the preparation is apt to receive the influence by changes of circumstances such as temperature, etc. For example, even if the preparation has a good quality just after preparing it, with the passage of time there is a possibility that drug-

release pattern becomes different from one at the earlier time because turobuterol crystallizes in the adhesive layer or changes of the concentration occurs.

In general essential physical properties such as adhesivity and shape retention of a patch is broken down and it is impossible to stably release the drug when a large amount of ingredients, which are either essential or unessential, are contained in the patch.

In regard to a patch containing much amount of turobuterol, when the amount of an adhesive is too much, the essential physical properties becomes worse and during application of the patch, it gives an uncomfortable feeling to a patient and there is also a possibility to drop it out due to rubbing with clothes.

Further, in regard to a patch in which turobuterol is much dissolved in the higher concentration, it can not help containing much amount of turobuterol and therefore, it is neither economical nor practical.

On the other hand, a patch in which both soluble type turobuterol and crystalline type turobuterol are contained in the specific rates (see Japanese Patent No. 2753800), a patch prepared by recrystallizing turobuterol in an adhesive (see WO97/14411), a patch consisting of turobuterol and a specific co-polymer, wherein turobuterol is suspended or microcapsulized and they are included in the adhesive layer, or a patch prepared by constructing matrix layers, adhesive layers or reservoir layers, and by laminating theses layers (see Japanese Patent No. 2633089), etc., were proposed as a dermally absorbable type patch which is aimed for a long lasting preparation of turobuterol.

However, in regard to these patches, when they are preserved for long time, they are apt to receive the influence by changes of

circumstances such as temperature, etc. For example, owing to the temperature rising in summer, turobuterol in crystals, suspensions or microcapsules contained in the patch dissolves and on the contrary, owing to the temperature dropping in winter, the dissolved turobuterol begins to crystallize. Also in case of laminated type preparations, owing to changes of circumstances, movement (transfer) of ingredients such as turobuterol and other ingredients occurs between matrix laminated layers and reservoir-layers, and the release pattern of turobuterol from the patch is changed and there is a possibility to give the influence to the therapeutic effect of turobuterol.

As well, these patches require complex techniques for suspending turobuterol, microcupsulation of it and stable blending it into the matrix, and selection of the condition for recrystalization of it in the matrix, construction of the matrix and the reservoir layer, laminating, etc. They are problematic.

DISCLOSURE OF INVENTION

The object of the present invention is to provide a patch in which turobuterol is contained in the lower concentration, but the patch has controllability of stable drug-release.

The present inventors have been extensively studied in consideration of the above problems and as a result, have found that a patch prepared by containing turobuterol in the lower concentration in an adhesive layer which was prepared by suitably combining a higher fatty acid, a rubber, an adhesive resin and a plasticizer, shows unexpectedly the drug-release in therapeutically effective amount and an ability to easily control drug-releasing pattern, is hardly influenced by changes of the passage with time and furthermore, has essential

physical properties such as adhesivity and shape pretension which are adjustable, and the process for preparation thereof is simple. Thus the present invention has been completed.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows changes of a passage with time of turobuterol-serum concentration in case of applying patches of Example 1 and Comparative example 1.

Figure 2 shows changes of the passage with time of turobuterol-permeability on extracted rat-skin in case of applying patches of Example 1, Comparative example 2 and Comparative example 3.

Figure 3 shows changes of the passage with time of turobuterol-permeability on extracted rat-skin in case of applying patches of Example 1, Comparative example 1, Comparative example 4 and Comparative example 6.

Figure 4 shows changes of the passage with time of turobuterol-permeability on extracted rat-skin in case of applying patches of Example 4 and Comparative example 5.

BEST MODE FOR CARRYING OUT THE INVENTION

Namely, the present invention relates to a patch containing turobuterol prepared by laminating an adhesive layer consisting of a rubber, an adhesive resin and a plasticizer on a backing, wherein 1 to 4 w/w % of turobuterol as an active ingredient and 0.1 to 3 w/w % of a higher fatty acid, preferably C_{11-22} fatty acid, especially preferably C_{14-18} fatty acid as a drug-release controlling agent are contained in the said adhesive layer.

The present invention also relates to a patch containing

turobuterol, wherein 5 to 35 w/w % of the rubber, 20 to 70 w/w % of the adhesive resin and 5 to 60 w/w % of the plasticizer are contained in the above adhesive layer.

In regard to patches containing turobuterol which have been traditionally proposed, it has been considered that it is essential to blend an acrylic adhesive which has a large polar or reactive group, or an adhesive resin having a large polarity such as a rosin in an adhesive layer.

However the patch related to the present invention does not need such substances, and that it is found that to blend such substances in an adhesive layer is not rather preferable because such substances cause to give great influences to release pattern of turobuterol and stability in changes of the passage with time.

The constitution of the patch preparation of the present invention is illustratively explained below.

Turobuterol which is contained as an active ingredient in the preparation of the present invention is dermally absorbed and exhibits an effect as a bronchodilator, and the preparation is characterized in containing turobuterol in its small amount of 1~4 w/w %. When the amount is less than 1 %, the area of application must be broadened in order to make the therapeutic effects exhibit. When the amount is beyond 4 w/w %, it is necessary to admix other ingredients to control the drug-release because the concentration of the drug becomes high and the drug is contained much. And as a result, there is a possibility to break down essential physical properties as a patch. These amounts therefore, are not preferable.

The higher fatty acid admixed in the present preparation has an activity to stably control release pattern of turobuterol, and is used for

the drug-release controlling agent. The higher fatty acid includes C_{11-22}, preferably C_{14-18} fatty acid, such as linolic acid, linolenic acid, oleic acid, stearic acid, palmitic acid, lauric acid, myristic acid, isostearic acid, ricinolic acid, etc., especially preferably oleic acid and stearic acid.

The amount is 0.1~3 w/w %, preferably 0.2~2 w/w %, more preferably 0.3~1 w/w %. When the amount is less than 0.1 w/w %, turobuterol is quickly released, and when the amount is beyond 3 w/w %, the drug-release is excessively controlled. Therefore these amounts are not preferable.

The rubber admixed in the present preparation has an ability to control the strength of an adhesive. The rubber includes a natural rubber, a synthetic rubber, such as isoprene rubber, styrene-butadiene rubber, styrene·butadiene block copolymer, styrene·isoprene block copolymer, preferably a synthetic rubber from the viewpoint of quality, especially preferably styrene·isoprene block copolymer.

The amount is usually 5~35 w/w %, preferably 10~30 w/w %, especially preferably 15~25 w/w %. When the amount is less than 5 w/w %, the strength of the adhesive does not become enough, and when the amount is beyond 35 w/w %, the strength becomes too high and the sticking power decreases.

The adhesive agent admixed in the present preparation has an ability to control the adhesive strength of an adhesive. The adhesive agent includes petroleum resin, polyterpene resin, polyolefin resin, saturated alicyclic hydrocarbon resin, etc., especially preferably petroleum resin, and saturated alicyclic hydrocarbon resin.

The amount is usually 20~70 w/w %, preferably 30~60 w/w %, especially preferably 40~55 w/w %. When the amount is less than 20 %, the adhesivity of the adhesive agent does not become enough,

and when the amount is beyond 70 w/w %, the sticking power becomes too high. Therefore, these amounts are not preferable.

The plasticizer admixed in the present preparation has an ability to control the viscosity of the adhesive and is used to delicately control essential physical properties, such as sticking power, strength and improvement of sensibility. The plasticizer includes a liquid resin, an oil, liquid paraffin, polybutene, etc., especially preferably liquid paraffin and polybutene.

The amount is usually 5~60 w/w %, in accordance with the amounts of a rubber and an adhesive agent contained.

The preparation of the present invention is prepared by wrapping the adhesive layer having the above mentioned constituents with both a backing and a release liner. The weight of the adhesive layer is 20~200g/m^2, preferably 50~150 g/m^2. When the weight is less than 20g/m^2, the sticking power becomes very weak and when the weight is beyond 200g/m^2, the sticking power becomes excessively strong and therefore, there is a possibility to injure the applied skin. Furthermore, to increase the weight without any object is not preferable from the economical viewpoint.

The backing is not limited as long as it is usually used and thereon an adhesive can be extended. However, a preferable backing is one that does not give excessively undesirable feeling to the skin during application and fully keep the adhesive in order not to remain on the skin when releasing off. Also the preferable backing is one which does not absorb turobuterol, such a polyester film as polyethyleneterephthalate (PET), a polypropylene film, and paper, a fabric, or an unwoven fabric laminated on thereon.

The liner is preferable one which does not absorb turobuterol,

such a polyester film as polyethyleneterephthalate (PET) etc., or its laminated film. The liner is preferable easily releasable from an adhesive when it is released. If necessary, a release agent such as silicon resin may be spread on the adhesive surface of the liner.

The suitable method for preparing the present preparation is a dry method. For example, constituents of an adhesive are dissolved in an organic solvent and the resulting solution is uniformly spread out on the one side of the liner. The treated liner is dried to remove the solvent and is stuck on the backing. Thus prepared patch is cut in a suitable size to be packed in a sealed package.

A hot-melt method as another method is considered. Namely the constitutions of an adhesive are blended and melted at about 100~200°C and then, spread on the liner at the same temperature. The preparation is cooled to prepare a patch.

This method has a merit in the viewpoint not to use an organic solvent, but the constituents are denatured to some extent as the heat charge is very large. Therefore, essential physical properties and the release pattern of turobuterol, etc., becomes unstable and the high processing technique is necessary for preparing it. Therefore, this method can not be chosen as the first option from the practical viewpoint.

Example

The present invention is explained by illustrating examples and test-examples, but the present invention is not limited by these examples.

Example 1

Adhesive	Content (w/w %)
Turobuterol	2
Oleic acid	0.5
Styrene·isoprene· styrene block copolymer	20
Saturated alicyclic hydrocarbon (Petroleum resin)	48
Polybutene	10
Liquid paraffin	19
Dibutylhydroxytoluene	0.5
Weight of adhesive	100g/m^2
Backing	PET 10μm
Liner	PET 75μm (Release coating on one side)

According to the above indications, turobuterol and oleic acid were dissolved in a suitable amount of toluene (Solution A). On the other hand, styrene·isoprene·styrene block copolymer, saturated alicyclic hydrocarbon resin, polybutene, liquid paraffin and dibutylhydroxytoluene were mixed with a suitable amount of toluene until being homogenous (Mixture B).

The solution A and the mixture B were stirred until being homogenous, and the mixture was spread on the release coated surface of the polyethyleneterephthalate (PET) liner in the amount of 100g/m^2 and dried. The PET backing was laminated on the adhesive side of the liner and the product was cut in a suitable size to be packed in a sealed package.

Example 2

Adhesive	Content (w/w %)
Turobuterol	2.5
Oleic acid	1
Styrene·isoprene· styrene block copolymer	25
Saturated alicyclic hydrocarbon resin (Petroleum resin)	43
Polybutene	8
Liquid paraffin	20
Dibutylhydroxytoluene	0.5
Weight of adhesive	125g/m²
Backing	PET 3.5μm/paper
Liner	PET 75μm (Release coating on one side)

According to the above indications and in the same manner as in the method of Example 1, a patch was prepared.

Example 3

Adhesive	Content (w/w %)
Turobuterol	2
Stearic acid	0.7
Styrene·isoprene· styrene block copolymer	18
Saturated alicyclic hydrocarbon resin (Petroleum resin)	50
Polybutene	5
Liquid paraffin	23.8
Dibutylhydroxytoluene	0.5
Weight of adhesive	90g/m²
Backing	PET 3.5μm／Unwoven fabric
Liner	PET 75μm (Release coating on one side)

According to the above indications and in the same manner as in the method of Example 1, a patch was prepared.

Example 4

Adhesive	Content (w/w %)
Turobuterol	3
Oleic acid	0.5
Styrene·isoprene· styrene block copolymer	20
Saturated alicyclic hydrocarbon resin (Petroleum resin)	42
Polybutene	10
Liquid paraffin	23.5
Dibutylhydroxytoluene	1.0
Weight of adhesive	80g/m^2
Backing	PET 12μm
Liner	PET 75μm (Release coating on one side)

According to the above indications and in the same manner as in the method of Example 1, a patch was prepared.

Comparative example 1

The commercially available crystalline type turobuterol patch (Trade name: Hokunalin tape prepared by Hokuriku Seiyaku K.K.): Turobuterol: 10 w/w %, 2mg/sheet, size of sheet: 10cm^2

Comparative example 2

By using the same ingredients as in Example 2 provided that in place of the oleic acid 1 w/w %, liquid paraffin 1 w/w % was used, a patch was prepared in the same manner as in the method of Example 1.

Comparative example 3

By using the same ingredients as in Example 2 provided that in place of saturated alicyclic hydrocarbon 43 w/w %, rosin glycerin ester 43 w/w % was used, a patch was prepared in the same manner as in the method of Example 1.

Comparative example 4

Adhesive	Content (w/w %)
Turobuterol	5.5
Styrene·isoprene· styrene block copolymer	56.8
Diolefin·olefin copolymer	37.7
Weight of adhesive	250g/m²
Backing	PET 25μm
Liner	PET 75μm (Release coating on one side)

According to the above indications, styrene·isoprene·styrene block copolymer and diolefin·olefin block copolymer were stirred at 150°C. Thereto was added turobuterol and the stirred mixture was passed through between release treated PET liner and PET backing during being kept at 110°C and it was rolled under the constant pressure in order to become 250g/m² in thickness. The obtained patch was cut in a suitable size to be packed in a sealed package.

This preparation is a highly concentrated, highly contained and soluble type turobuterol patch prepared by the method of example (sample 2a) of Japanese Patent No. 2633089.

Comparative example 5

Adhesive	Adhesive layer 5-1 Content (w/w %)	Adhesive layer 5-2 Content (w/w %)
Turobuterol	1	5.5
Styrene·isoprene· styrene block copolymer	61.3	56.8
Diolefin·olefin copolymer	37.7	37.7
Weight of adhesive	50g/m²	200g/m²
Backing	PET 25μm (Release coating on one side)	PET 25μm (Release coating on one side)
Liner	PET 75μm (Release coating on one side)	PET 75μm (Release coating on one side)

According to the above indications, an adhesive layer 5-1 and an adhesive layer 5-2 were prepared in the same manner as in Comparative example 4. After removing each PET backing, each adhesive surface was stuck each other to prepare a laminated turobuterol patch preparation. The preparation was cut in a suitable size to be packed in a sealed package.

This preparation is a laminated and soluble type turobuterol patch prepared by the method of Japanese Patent No. 2633089.

Comparative example 6

Adhesive	Content (w/w %)
Turobuterol	5
Isopropyl myristate	40
Styrene·isoprene· styrene block copolymer	38.5
Polyisobutylene	5.5
Saturated alicyclic hydrocarbon resin (Petroleum resin)	11
Weight of adhesive	40g/m^2
Backing	PET 25μm
Liner	PET 75μm (Release coating on one side)

According to the above indications, styrene·isoprene·styrene block copolymer, polyisobutylene and saturated alicyclic hydrocarbon resin were mixed until being homogenous. To the mixture were added and mixed turobuterol and isopropyl myristate until being homogenous. The solution was spread on the surface of release treated PET in the amount of 40g/m^2 dried and stuck on PET backing. Thus obtained preparation was cut in a suitable size to be packed in a sealed package.

This preparation was a highly concentrated and soluble type turobuterol patch prepared by example 8 of Japanese Patent Publication A 11-228395.

Test 1

A patch of Example 1 (turobuterol: 2 w/w %, size: 10cm^2) and a commercially available patch of Comparative example 1 were applied to the back of a hair-cut rat respectively. Two, four, eight, ten and twenty four hours later, the blood was taken and turobuterol levels in serum were measured by HPLC. Changes of the passage with time of

turobuterol levels in serum on application of patches of Example 1 and Comparative example 1 were shown in Fig. 1.

From this test result, it was suggested that a patch of Example 1 maintained for a long time turobuterol levels in serum as same as the commercialized patch of Comparative example 1, which contains 5 times amount of turobuterol as much as the patch of Example 1 has. Therefore, it was shown that the patch of the present invention was a lower concentrated and soluble type patch, and had an ability to control the drug-release for a long time.

Furthermore, according to the disclosure of WO 97/14411, the crystalline type turobuterol patch requires to adjust the average particle size of turobuterol within 2~20μm, in order to stabilize the drug-release from the patch and its duration. Therefore, due to crystallizing turobuterol during adjusting the particle size in the adhesive layer, the ageing process for controlling time and temperature is required.

On the contrast, the patch of Example 1 is a lower concentrated and soluble type turobuterol patch and has drug-release ability without containing its crystals. Therefore, it was cleared that the process for preparing for this patch did not require the above mentioned complex ageing processes and the patch could be prepared by a very simple procedure.

Test 2

The skin of abdomen of a hair-cut rat was extracted and fitted on a Frantz-diffusion cell. Phosphate-buffer was used as a reservoir solution and the cell was kept to stir at 37°C during test.

A patch of Example 1, and patches of Comparative examples 2 and 3 were cut in a circle having diameter 13mm (Turobuterol of

Example 1 and Comparative examples: 2 w/w %, 200μg/cm^2), and the circles fitted on the extracted skin. Small amount of the reservoir solution was from time to time taken and the amount of permeated turobuterol was measured by HPLC (Drug permeation test on rat-extracted skin).

Changes of the passage with time of permeated turobuterol in case of application of patches of Example 1 and Comparative examples 2 and 3 were shown in Fig 2.

Example 1: turobuterol; 2 w/w %, 200μg/cm^2

Comparative example 2 and 3: turobuterol; 2 w/w %, 200μg/cm^2

From this test result, the amount of permeated turobuterol in regard to the patch of Example 1 was constant in changes of the passage with time. On the other hand, in regard to the patch of Comparative example 2 without containing a higher fatty acid, it showed the tendency that the amount of the permeated drug increased and the duration decreased at a latter half. Furthermore, in Comparative example 3 containing rosin glycerin ester having polarity, the drug permeability greatly decreased.

Test 3

Influence on drug-release by preservation temperature

In order to check the influence on drug-release due to the changes of preservation temperature, patches of Example 1, Comparative examples 1, 4 and 6 were preserved in incubator kept at 4°C and 40°C respectively for 3 weeks, and then the temperature was adjusted to room temperature. In the same manner as Test 2 the drug permeation test on the skin extracted from rat was carried out.

In case of application of patches of Example 1, Comparative

examples 1, 4 and 6, changes of the passage with time of the permeation of turobuterol were shown in Fig. 3. The drug-permeation rate due to changes of preservation temperature was shown in Table 1.

Example 1: turobuterol; 2 w/w %, 200μg/cm²

Comparative example 1: turobuterol; 10 w/w %, 200μg/cm² (Crystalline type turobuterol patch)

Comparative example 4: turobuterol; 5.5 w/w %, 1375μg/cm² (Highly concentrated, highly contained and soluble type turobuterol patch)

Comparative example 6: turobuterol; 5 w/w %; 200μg/cm² (Highly concentrated and soluble type turobuterol patch)

Table 1

Rate of drug permeated amount due to changes of preservation temperature on each sample

Test example	Example 1	Comparative example 1	Comparative example 4	Comparative example 6
Rate of permeation	89 %*	65 %	162 %	44 %

*Example of calculation: {permeation amount of Example 1 (4°C) (8 hr)} / {permeation amount of Example 1 (40°C) (8 hr)} × 100

From this test result, it was shown that the drug permeated amount on a patch of Example 1 was constant and hardly influenced by changes of preservation temperature.

On the other hand, it was shown that the group of Comparative examples was apt to receive the influence by the changes of preservation temperature.

This fact suggested that due to changes of preservation

temperature, the rate of crystals and dissolved portion in the adhesive was changed and due to the high concentration of the drug, the degree of saturation in the adhesive was changed, or since the drug was easy to separate from the constituents of the additive, it was possible that the amount of permeation of the drug was greatly changed up and down.

Test 4

Influence on drug-release by preservation term

In order to see the influence on drug-release by preservation term, by using two kinds of patches of Example 4, which was prepared 12 hours before and which was preserved for 2 months at room temperature, and two kinds of patches prepared by sticking layers 5-1 and 5-2 in Comparative example 5, which was prepared 12 hours before, and which was preserved for 2 months at room temperature, in the same manner as in Test 2, the drug permeation test on the skin extracted from rat was carried out. In regard to patches of Comparative example 5, the 5-1 layer side which was lower in the drug concentration was applied to the skin.

Changes of the passage with time of permeated turobuterol in case of application of patches of Example 4 and Comparative example 5 were shown in Fig 4.

Example 4: turobuterol; 3 w/w %, 240 μg/cm^2

Comparative example 5: (adhesive layer 5-1) turobuterol; 1 w/w %, 50 μg/cm^2 + (adhesive layer 5-2) turobuterol; 5.5w/w %, 1108μg/cm^2 (laminated patch)

From this test result, it was shown that a patch of Example 4 was constant in drug permeation amount with changes of the passage with time.

On the other hand, in regard to a patch of Comparative example 5, the drug permeation amount was increased with changes of the passage with time. Even if the adhesive had the higher drug concentration, the drug permeation amount was controllable by sticking the layers having the lower drug concentration, but it was considered that the transfer between adhesive layers occurred and the concentration of the drug was averaged during a long time and therefore the control of the drug-release was injured.

INDUSTRIAL APPLICABILITY

The patch of the present invention is prepared by dissolving turobuterol in the lower concentration in an adhesive layer and thereto adding a higher fatty acid, a rubber, an adhesive agent and a plasticizer in a suitable amount respectively, can easily control the turobuterol release pattern and is excellent in changes of the passage with time of release pattern.

Furthermore, according to the present invention, essential physical properties on a patch such as adhesivity and shape retention is suitably adjusted and by simplifying the method for preparation, the patch of the present invention has following advantages comparing with the known turobuterol-patch:

(1) Despite fact that the content of turobuterol is less, the effect can be optimized according to the therapeutic object as the patch of the present invention shows sufficient turobuterol release amount and it is possible to widely and simply control the turobuterol release amount.

(2) The adjustment of essential properties as a patch is possible together with controlling the release amount and releasing pattern of turobuterol. Therefore, it becomes possible to provide a patch which is

therapeutically effective and has physical properties suitable to the skin condition.

(3) During preservation, the influence by changes of circumstances is less and the quality is stably kept for a long term.

(4) The preparation method is very simple and practical.